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HYPobaric HYPOXIA (380 TORR) DECREASES
INTRACELLULAR AND TOTAL BODY WATER IN GOATS

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ABSTRACT

The effect of 16 days of hypobaric hypoxia (380 Torr, 5500 m) on body fluid distribution was studied in four unanesthetized adult goats (Capra lircus). Total body water (TBW), extracellular fluid volume (ECF), and plasma volume (PV) were determined with ³H₂O, [¹⁴C]-inulin, and indocyanine green, respectively. Blood volume (BV = PV x 100/[100 - hematocrit]), red cell volume (RCV = BV - PV), intracellular fluid (ICF = TBW - ECF) and interstitial fluid (ISF = ECF - PV) volumes were calculated. Body mass (-7.1%), TBW (-9.1%), and ICF volume (-14.4%) decreased, while ECF (+11.7%) and ISF (+27.7%) volumes increased with exposure ($p < 0.05$). The decrease in TBW accounts for 89% of the loss of body mass. Hematocrit increased from 24.0 \pm 1.0% SEM to 34.2 \pm 2.2% ($p < 0.05$). BV was unchanged; an increase in RCV (+39.5%) counterbalanced the decrease in PV (-15.3%) ($p < 0.05$). Goats were similar to humans in that prolonged hypobaric hypoxia resulted in decreases in TBW volume, ICF volume, and PV.

Index terms: high altitude; total body water; extracellular fluid; plasma volume; RER



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INTRODUCTION

Although hypoxia markedly alters body water metabolism, there is disagreement about its effects on total body water (TBW), intracellular water, and body fluid distribution. For instance, prolonged exposure to hypoxia, i.e. 6-14 day at 3500-5334 m elevation, results in a negative fluid balance (5) and decreased TBW (16,17,19,24). There are also reports of decreases in extracellular fluid (ECF) volume (8,11,12,16,20,24), and intracellular fluid (ICF) volume (ICF = TBW - ECF) (16,17,19,21,24). However, prolonged hypoxia is also reported to result in little or no change in TBW (8,11,12,25), increased ICF volume, and ECF redistribution into the ICF compartment (8,11,12). The conflicting findings in these latter studies may be due to technical difficulties accurately estimating TBW from the pattern of tracer elimination following bolus administration of 4-aminoantipyrine (8,11,12) or D₂O (12,25).

A decrease in plasma volume (PV) with prolonged hypoxia has consistently been demonstrated in humans with either radioactively labeled albumin or dye dilution techniques (11,16,17,18,24,25). Reported interstitial fluid (ISF = ECF - PV) volume changes with hypoxia, however, are inconsistent, reflecting the difficulty defining and measuring ECF volume (8,12,11,16,17,19,20,21,24).

Because of these contradictions, a clear description of fluid redistribution with hypoxia was needed to facilitate research on the neurohormonal control of body fluid volumes (15) and on the origins of the pulmonary and cerebral edema that can occur at high terrestrial elevations (10). Therefore, we measured gas exchange, TBW, and body fluid distribution in full-grown goats at sea level and after 16 days of hypobaric hypoxia (5500 m). TBW, ECF volume, and PV were measured using $^3\text{H}_2\text{O}$, [^{14}C]-inulin, and indocyanine green dye, respectively. We hypothesized that a 16 day exposure to simulated altitude would result in a loss of TBW associated with decreases in both ICF volume and PV.

METHODS

Four adult female goats (*Capra lircus*) were surgically prepared more than one month prior to the experiment by externalizing denervated carotid and jugular loops for sampling arterial and venous blood. The goats were kept on a light/dark cycle of 12h/12h. The animals had ad libitum access to water and were fed a daily ration of approximately 450 grams of a mixture of rolled oats, cracked corn, molasses, and pelleted alfalfa (Purina Chow No. 14) and about 600 grams of a loose mixture of alfalfa/timothy hay.

Measurements of gas exchange, blood gases, blood composition,

and body fluid distribution were made at sea level and after 16 days of hypobaric hypoxia. The goats were at least 15 h post-prandial and did not have access to water during testing. After sea-level measurements were complete, the chamber was decompressed to a pressure of 380 Torr \pm 2 (5500 m), at a rate of 610 m \cdot min $^{-1}$. The chamber was maintained at 24 \pm 1 °C, and 50 \pm 5 % relative humidity. Fractional CO₂ concentration was always less than 0.004. After the 16th day of uninterrupted exposure, measurements of gas exchange, blood gases, blood composition, and body fluid distribution were repeated.

Gas exchange. A snug latex mask with a low resistance valve (Model 2700, dead space 90 cc, Hans Rudolph Inc., Kansas City, MO), and an automated metabolic system (MMC Horizon Cart, Sensor Medics, Inc., Anaheim, CA) were used to measure resting ventilation ($\dot{V}E$), oxygen consumption ($\dot{V}O_2$), and CO₂ production ($\dot{V}CO_2$). The animals had previously been habituated to the mask and therefore remained calm during all measurements. Alveolar ventilation (V_A) was calculated using Enghoff's modification of Bohr's formula for respiratory dead space (7). The portion of total $\dot{V}O_2$ attributable to fat oxidation was estimated from the respiratory exchange ratio (RER = $\dot{V}CO_2/\dot{V}O_2$) and the equation: $\dot{V}O_2$ for fat = (total $\dot{V}O_2$) (1 - RER)/0.3. The $\dot{V}O_2$ for carbohydrate oxidation was equal to the difference between the $\dot{V}O_2$ for fat oxidation and the total $\dot{V}O_2$. Protein oxidation was

assumed to be negligible.

Blood gases and blood composition. When steady state gas exchange was evident from the mixed expired and end-tidal PCO_2 , samples of arterial blood were collected anaerobically for measurement of PO_2 , PCO_2 , and pH. Blood gases and pH were measured at 37°C with a calibrated Radiometer blood gas analyzer (Model ABL-300, Radiometer, Copenhagen, Denmark) and corrected to body temperature as measured by a rectal thermistor. Hematocrit (Hct) was determined in duplicate with microcapillary tubes and a microcapillary centrifuge and tube reader (International Equip. Co., Needham Heights, MA). Hemoglobin was measured in duplicate with a hemoglobinometer (Coulter Electronics, Hialeah, FL) accurate to 0.2 $\text{g} \cdot \text{dl}^{-1}$. Total plasma protein concentration (TP, $\text{g} \cdot \text{dl}^{-1}$) was measured with a refractometer (American Optical/Reichert, Buffalo, NY). Plasma osmolality was measured by freezing point depression (Fiske Assoc., Needham, MA). Total plasma protein mass (TPM) was calculated as $\text{TPM} = \text{PV} \times \text{TP}$.

Fluid distribution. After gas exchange, blood gas, and blood composition measurements were completed, TBW, ECF volume, and PV were determined as previously described (6). Intracellular and interstitial fluid volumes were calculated as $\text{ICF} = \text{TBW} - \text{ECF}$, and $\text{ISF} = \text{ECF} - \text{PV}$, respectively. Total blood volume ($\text{BV} = \text{PV} \times (100/100 - \text{Hct})$) and red cell volume ($\text{RCV} = \text{BV} - \text{PV}$) were calculated

(9) without correcting Hct for trapped plasma or calculating whole body Hct.

Each unanesthetized, fully conscious goat was injected intravenously with 1 ml of physiological saline containing $2.3 \text{ nCi} \cdot \text{H}_2\text{O} \cdot \text{kg}^{-1}$ body wt (New England Nuclear, Boston, MA). After a 120-min equilibration period a 3 ml blood sample was taken for the determination of TBW. Next, ECF volume was measured by intravenously injecting [^{14}C]inulin ($2.2 \text{ nCi} \cdot \text{kg}^{-1}$ body wt in 1 ml saline, New England Nuclear, Boston, MA), collecting 1.0 ml arterial blood samples at 2, 4, 6, 30, 60, and 90 min, and analyzing the decay pattern. PV was determined by concurrently injecting 2 mg in 1 ml saline of indocyanine green (ICG) (Hynson, Westcott, and Dunning, Div. of Becton Dickenson, Rutherford, NJ), collecting separate 1 ml arterial blood samples at 2, 4, and 6 min, and analyzing the pattern of decay. The total volume injected (3 ml) and the total volume of blood removed for analysis (12 ml) were kept to a minimum to avoid disturbing fluid balance.

Blood samples, collected in heparin and maintained at 5°C , were centrifuged and analyzed promptly. Plasma $^3\text{H}_2\text{O}$ and [^{14}C]inulin specific activity was determined with a Beckman LS8000 series liquid scintillation system (Waldwick, NJ) using a standard library program for dual labels. A Hitachi Model 1200-60 spectrophotometer (Danbury, CT) was used to measure ICG concentration.

Statistical analysis. Values are presented as means \pm SEM. Student's paired T-test (two-tailed) was used to assess the significance of differences between values. The null hypothesis was rejected at $p < 0.05$.

RESULTS

Gas exchange. Respiratory and arterial blood gas data are summarized in Table 1. The changes in resting minute ventilation, alveolar ventilation, $\dot{V}CO_2$, and $\dot{V}O_2$, from sea level to hypoxia were not statistically significant. However, there was a significant increase in the mean resting respiratory exchange ratio from 0.78 to 0.88 ($p < 0.05$). There were also decreases in $PaCO_2$ and PaO_2 , and an increase in arterial pH ($p < 0.05$) (Table 1).

Body fluid redistribution. The effects of 16 days of hypobaric hypoxia on body mass and the volumes of major body fluid compartments are summarized in Table 2. With the exception of BV, which was unchanged, the volumes of all the fluid compartments listed in Table 2 changed significantly with prolonged hypoxia ($p < 0.05$). Changes in Hct, and fluid compartment volumes (liters), and in fluid compartment spaces, i.e. relative compartment volume expressed as $ml \cdot kg^{-1}$ body mass, were similar to those previously reported for sheep exposed to 348 Torr (6200 m) for 32 days (21).

There were decreases in the volume of TBW (-9.1%, -3.16 l),

ICF (-14.4%, -3.87 l), and PV (-15.3%, -0.40 l), and increases in ECF volume (+11.7%, +0.89 l), ISF volume (+22.7%, +1.38 l), and RCV (+39.5%, +0.32 l) (Table 2). Although there was a 0.40 l decrease in PV, the associated decrease in BV (-0.08 l) was insignificant due to an offsetting 0.33 l increase in RCV (Table 2).

Relative changes in fluid compartments^{spaces} were similar whether they were expressed as $\text{ml} \cdot \text{kg}^{-1}$ body weight, or as $\text{ml} \cdot \text{l}^{-1}$ TBW. TBW space, i.e. TBW volume per kg body mass, was unchanged with an overall mean of $687 \pm 8 \text{ ml} \cdot \text{kg}^{-1}$. ICF decreased 8.4% from 541 ± 8 to $496 \pm 14 \text{ ml} \cdot \text{kg}^{-1}$; ECF increased 20.1% from 153 ± 9 to $184 \pm 6 \text{ ml} \cdot \text{kg}^{-1}$; ISF increased 35% from 101 ± 7 to $136 \pm 7 \text{ ml} \cdot \text{kg}^{-1}$ ($p < 0.05$). BV was unchanged at $72 \pm 4 \text{ ml} \cdot \text{kg}^{-1}$, and PV was unchanged at $51 \pm 2 \text{ ml} \cdot \text{kg}^{-1}$.

Blood composition. The changes in total plasma protein (TP, g/dl), total plasma protein mass (TPM, g), plasma osmolality, hemoglobin (Hb), and hematocrit (Hct), are summarized in Table 3. TP and plasma osmolality were unchanged, while calculated TPM decreased along with PV (Table 3). The increase in Hct appeared to be due to both an increase in red cell volume and a decrease in PV. Mean cell Hb concentration, i.e. Hb concentration $\times 100/\text{Hct}$, was unchanged.

DISCUSSION

Gas exchange. The respiratory and arterial blood gas data summarized in Table 1 are consistent with previous reports. Goats exposed to 450 Torr (4300 m) for 14 days showed a similar increase in arterial pH, and similar decreases in PaCO_2 , and PaO_2 (26). The decrease in $\dot{V}o$, with hypoxia in the goats (Table 1) is consistent with a previous report of decreased $\dot{V}o$, at altitude in lambs (23).

An increase in resting RER from 0.74 to 0.89 (Table 1), indicates a shift from a fat-predominant fuel metabolism at sea level (73% fat:27% carbohydrate) to a carbohydrate-predominant fuel metabolism with hypoxia (40% fat:60% carbohydrate). Although little information is available on changes in human RER at high altitude, a resting RER of 0.88 has been reported in sheep exposed to 348 Torr (6200 m) for 32 days (21). Although this indicates a carbohydrate-predominant fuel metabolism, an elevated resting sea-level RER of 1.03 in these sheep led Phillips and coworkers (21) to the opposite conclusion that there was a shift from a carbohydrate-to a fat-predominant fuel metabolism. However, an RER above 1.0 suggests that hyperventilation prevented an accurate assessment of sea-level fuel metabolism. A carbohydrate-predominant fuel metabolism may be adaptive at high altitude since the energy yield per liter of oxygen increases when proportionally more carbohydrates are combusted.

Body fluid redistribution. Prolonged exposure to elevations greater than 3500 m generally results in reduced body weight, negative total body fluid balance (5,19), and decreased TBW volumes (16,17,19,21,24). Our results are consistent with these findings (Table 2).

Decreased TBW accounted for about 89% of the decrease in body mass in the goats (Table 2), and 60% of the decrease in body mass in sheep exposed to 348 Torr for 32 days (21). Changes in body composition due to decreased food intake (21) probably account for the balance of the decrease in body mass. There were decreases in the absolute volume of TBW, ICF, and PV, and increases in ECF and ISF volumes, in both goats (Table 2) and sheep (21).

Prolonged hypoxia has similar effects on the body fluid spaces of goats, and sheep (21). Fluid space is defined here as fluid volume per unit body weight ($\text{ml} \cdot \text{kg}^{-1}$), although it can also be expressed relative to TBW ($\text{ml} \cdot \text{l}^{-1}$). As was evident with absolute volume changes, ICF space decreased, and ECF and ISF spaces increased significantly. In contrast to the decreases in absolute TBW and PV (Table 2) (21), TBW space, and plasma space were unchanged by hypoxia (see Results) (21).

The effects of hypoxia on the total body water of small mammals has been studied directly by means of carcass desiccation (2,3,13). Growing rats exposed to 3475-4300 m for 24-26 days did

not exhibit a decrease in TBW space (2,3), whereas there was a significant loss of TBW space in adult mice exposed to hypoxia (4300 and 6100 m) for 2 to 7 days (13). The observation that hypoxia resulted in a loss of TBW space in full-grown mice, but not in growing rats, has been attributed to species differences, or to differences in growth rate (13).

In studies where TBW is calculated from equilibrium tracer concentrations following D₂O or ³H₂O administration, hypoxia results in 3.2 to 5.4% decreases in TBW volume, and 2.7 to 15.6% decreases in ICF volume (16,17,19,21,24) (Table 4). Whereas, when TBW is estimated from the pattern of tracer elimination following the bolus administration of AAP or D₂O, apparent TBW volume changes with hypoxia are in the -2.0% to +3.2% range, and apparent ICF volume increases 2.6 to 13.2% (8,11,12) (Table 4). These disparities, and the problems measuring TBW via bolus D₂O administration (11,25), may be due to difficulties accurately estimating TBW volume changes with bolus administration tracer techniques (27). Any errors in measuring TBW volume will naturally also compromise the accuracy of calculated ICF volume measurements.

The dynamics of tracer distribution have little effect on the measurement of TBW when equilibrium tracer methods are used (27). In contrast, when bolus administration tracer methods are used, equations accurately describing the decline in tracer levels are

needed to calculate TBW (27). Unfortunately, the complex compartmentalization of body water (4), and changes in circulatory distribution with hypoxia (14), make it very difficult to generate the correct equations needed to accurately estimate TBW. If hypoxia increased the time needed for tracers to equilibrate with the intracellular compartment, for example, the simple approach of analyzing tracer elimination as a single exponential curve could lead to an overestimation of TBW volume.

Measurements of ECF volume made with thiocyanate (8,11,12) and radiosulfate (16,20,24) suggest that lowlanders experience decreases in ECF volume, and probably decreases in ECF space (20), after two to twelve days at elevations of 3500 to 5300 m. In contrast, high-altitude residence is associated with an expanded ECF space, i.e. an increase in the fractional contribution of ECF volume to total body mass (17,22). ECF space, measured with $\text{Na}_2^{35}\text{SO}_4$, increased in highlanders after 12 days of re-exposure to 3500 m (17), while sucrose space was found to be larger in highlanders than lowlanders (22). ECF space and ECF volume, measured with Na^{36}Cl , increased in sheep after 32 days at 348 Torr (21). Similarly, ^{14}C -inulin ECF space and volume increased in the goats (Results, Table 2).

Our data indicate that the increase in ECF volume in the goats is the result of an expanded ISF compartment (Table 2). The

increase in ISF volume in the present study is similar to that in sheep after 32 days at 6200 m elevation (21). In contrast, several human studies suggest that hypoxia results in decreased (11,24) or unchanged (8,16,17) ISF volume. The peripheral edema evident in some humans at high altitude (10), however, suggests an increase in ISF volume can occur.

It has been consistently demonstrated that plasma volume (PV) decreases up to 30% at altitudes greater than 3500 m (11,16,17,18,24,25). There are usually decreases in BV and PV, and no change in RCV, in response to 8-12 days at 3500-4300 m (16,18,25). The PV of the goats in this study also decreased significantly, however, BV was unchanged because of a counterbalancing increase in RCV (Table 2). Hemoconcentration was not evident since plasma osmolality and TF concentration were unchanged (Table 3). In comparison, after 32 days at 348 Torr, sheep displayed a larger increase in RCV (+47.8%, +0.55 l), a smaller decrease in PV (-7.8%, -0.24 l), and, consequently, an increase in BV (+7.3%, +0.31 l) (21). This suggests that with more prolonged hypoxia, a similar pattern might be evident in the goats.

Presently, the mechanisms of body fluid loss and redistribution with hypoxia are not well understood. It is possible that aortic chemoreceptor stimulation and increased atrial natriuretic factor production with acute hypoxia (1,15) leads to

diuresis, natriuresis, and decreases in PV, BV, ECF, and ICF volumes.

In summary, 16 days exposure of adult goats to hypobaric hypoxia resulted in a loss of TBW volume associated with decreases in ICF volume and PV, and increases in ECF and ISF volumes.

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In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

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TABLE 1. Effect of 16 days of hypobaric hypoxia (380 Torr) on respiratory and arterial blood gas values of adult goats.

	\dot{V}_E ($l \cdot min^{-1}$)	\dot{V}_A ($l \cdot min^{-1}$)	\dot{V}_{O_2} ($ml \cdot min^{-1}$)	\dot{V}_{CO_2} ($ml \cdot min^{-1}$)	RER	$PaCO_2$ (Torr)	PaO_2 (Torr)	pH
<u>Sea level</u>								
SEM	8.42	4.44	237	174	0.74	34.4	84.8	7.408
SEM	0.63	0.44	25	16	0.02	1.3	2.2	0.007
<u>Hypoxia</u>								
SEM	11.40*	5.11*	165*	146	0.89*	24.9	26.8*	7.489*
SEM	1.05	0.55	16	12	0.02	0.7	1.7	0.013

Values are means \pm SEM, N = 4. Minute ventilation (\dot{V}_E); alveolar ventilation (\dot{V}_A); oxygen (\dot{V}_{O_2}); CO₂ production (\dot{V}_{CO_2}). *Different from sea-level control (p < 0.05).

TABLE 2. Effect of hypoxia on body mass and body fluid volumes.

	BM (kg)	TBW volume (1)	ICF volume (1)	ECF volume (1)	ISF volume (1)	BV (1)	PV (1)	RCV (1)
<u>Sea level</u>								
\bar{X}	49.80	34.57	26.79	7.60	4.99	3.43	2.62	0.81
SEM	0.96	0.65	0.79	0.33	0.30	0.11	0.07	0.06
<u>Hypoxia</u>								
\bar{X}	46.25*	31.41*	22.92*	8.49*	6.37*	3.35	2.22*	1.13*
SEM	1.54	1.01	1.00	0.20	0.25	0.20	0.10	0.12

Values are means \pm SEM, N = 4. Body mass (BM), total body water (TBW), intracellular fluid (ICF), extracellular fluid (ECF), interstitial fluid (ISF), blood volume (BV), plasma volume (PV), and red cell volume (RCV). *Different from sea-level control ($p < 0.05$).

Table 3. Effect of hypoxia on blood composition.

	TP (g·dL ⁻¹)	TPM (g)	Osm (mosmol·kg ⁻¹)	Hb (g·dL ⁻¹)	Hct (%)
<u>Sea level</u>					
X	7.1	188	295	8.8	24.0
SEM	0.2	5	1	0.6	1.0
<u>Hypoxia</u>					
X	7.3	163*	295	12.4*	34.2*
SEM	0.2	8	2	1.4	2.2

Values are means \pm SEM, N = 4. Total plasma protein (TP), total plasma protein mass (TPM), plasma osmolality (Osm), hemoglobin (Hb), and hematocrit (Hct). *Different from sea level control (p < 0.05).

Table 4. Effect of hypobaric hypoxia on TBW, ECF, and ICF volumes estimated with various techniques.

<u>Species</u>	<u>No.</u>	<u>Altitude</u>	<u>Duration</u>	<u>Method</u>	<u>TBW</u>	<u>ICF</u>	<u>ECF</u>	<u>Ref.</u>
Sheep	6	6200 m	32 d	c, i	-	-	+	21
Goats	4	5500 m	16 d	c, k	-	-	+	Table 2
Human	9	4300 m	2 d	g	NM	NM	-	20
Human	15	4300 m	12 d	a, d	NC/-	NM	NM	18
Human	12	4300 m	6 d	a	-	-	NC	19
Human	9	3500 m	12 d	c, g	-	-	-	16
Human	19	3500 m	12 d	c, g	-	-	NC	17
Human	10	3500 m	12 d	c, g	-	-	-	24
Human	4	4300 m	8 d	b	NC	NM	NM	25
Human	9	4300 m	14 d	b, e, h	+	+	-	11
Human	9	4300 m	14 d	e, h	NC	+	-	12
Human	8	5334 m	10 d	e, h	-	+	-	8

*Relatively small 0.8 l, 2% decrease. Key for methods: (a) Equilibrium D_2O ; (b) Bolus D_2O injection; (c) Equilibrium 3H_2O ; (d) Calculated from hydrostatic weight; (e) Bolus 4-aminoantipyrine injection; (f) Carcass desiccation; (g) Radiosulfate, $Na^{35}SO_4$; (h) Thiocyanate; (i) Radiochloride, $Na^{36}Cl$; (j) ICF and ECF calculated from total body potassium and chloride; (k) ^{14}C -inulin. Total body water (TBW), intracellular fluid (ICF), extracellular fluid (ECF), no measurement (NM), no change (NC).